## REMARKS

In the final Office Action mailed May 6, 2005, the Examiner imposed the following rejections of the pending claims:

1) the Examiner rejected Claims 1, 3, 5-8, 11, 14, and 16-19 under 35 U.S.C. §103 as being obvious over Krieg (U.S. Patent No. 6,207,646 ('646)) or Krieg (U.S. Patent No. 6,429,199 ('199)), taken with any of Wheeler *et al.* (U.S. Patent No. 5,981,501 ('501)), MacLachlan (WO 99/39741 ('741)) or Semple (WO 98/51278 ('278)); and

2) the Examiner rejected Claims 1, 3, 5-12, 14, and 16-19 under 35 U.S.C. §103 as being obvious over Krieg ('646) or Krieg ('199), taken with any of Wheeler *et al.* ('501), MacLachlan ('741) or Semple ('278), and further in view of Meers (U.S. Patent No. 6,143,716 ('716)).

Applicants respectfully traverse and request reconsideration in light of the remarks that follow.

## I. BRIEF STATEMENT OF THE INVENTION

Lipid–based vehicles have been disclosed previously in the art for the delivery of a wide variety of small and large molecule therapeutics, including chemotherapy agents, proteins, peptides and sequence-specific nucleic acids such as, *e.g.*, plasmids and antisense. Depending on the nature of the lipid composition selected, one can preferentially target particular cell types such as tumor cells or immune cells. Likewise, by varying the lipid composition one may also selectively deliver a desired therapeutic agent extracellularly (*e.g.*, to interstitial spaces) as well as intracellularly. In the case of intracellular delivery this can be, for example, either endosomal delivery or cytoplasmic delivery with subsequent access to sites such as the nucleus.

The selection of an appropriate lipid formulation depends to a great extent upon the nature of the therapeutic agent, its underlying biological mechanism of action and the particular

indication to be treated. In the case of small molecule anticancer drugs, for example, suitable lipid formulations are employed that extravasate through leaky blood vessels within tumors resulting in preferential carrier accumulation in the interstitial space. Encapsulated drugs are released into the extracellular medium and are then rapidly taken up by the surrounding tumor cells. For sequence-specific nucleic acids such as plasmid DNA or antisense, which are unable to permeate across the plasma membrane, the lipid formulation may be selected to deliver the nucleic acid into the cytoplasm, allowing subsequent access to the nucleus via passive diffusion. Thus, the selection of an appropriate lipid formulation typically depends upon and requires detailed knowledge of the pharmacokinetics and pharmacodynamics of the therapeutic agent to be delivered, as well as consideration of the site of action of the therapeutic agent.

Immune stimulatory sequences ("ISS") such as CpG oligonucleotides represent a newer class of therapeutic DNA molecules having, it turns out, a very distinct mechanism and site of action in comparison with sequence-specific nucleic acids. *See* Latz *et al., Nature Immunol.* 5:190-198 (2004) (reporting a previously unknown mechanism of cellular activation whereby TLR9 is recruited from the endoplasmic reticulum to sites of CpG uptake) (included as document C5 in the accompanying Supplemental Information Disclosure Statement). Significantly, however, the correlation between TLR9 and CpG signaling was not discovered until well after the priority date of the instant case, and even then was the subject of active academic debate. *Compare* Hemmi *et al. Nature* 408:740-745 (2000) (proposing involvement of a newly-discovered Toll-like receptor, TLR9, in CpG signaling) (included as document C3 in the accompanying Supplemental IDS) with Chu *et al. Cell* 103:909-18 (2000) (suggesting that a DNA-dependent protein kinase, DNA-PK, is required for CpG signaling) (included as document C1 in the accompanying Supplemental IDS). As noted by Hemmi *et al.*, the nature and

localization of the putative CpG receptor was still controversial in December of 2000, and there was evidence for both cell-surface activation by CpG as well as internalization of CpG. *Id.* at 743, 1st column. This lack of an adequate understanding of the mechanism or site of action of ISS such as CpG as of the priority date created significant uncertainty in the art as to how such molecules should be formulated for therapeutic delivery.

The present invention stems from the discovery that lipid-based delivery of immunostimulatory nucleic acid sequences ("ISS"), such as CpG dinucleotides, can lead to truly synergistic improvements in immune stimulatory activity depending on the nature of the lipid vehicle employed. As demonstrated in the specification and in the Declaration submitted by Applicants during prosecution, all lipid-based vehicles are not the same and do not provide uniformly beneficial results for this particular class of therapeutics. In comparison with conventional lipid delivery vehicles such as lipid complexes, Applicants' fully-encapsulated liposomal particles provide dramatic increases in immune stimulatory activity, including the generation of immune stimulatory activity even from non-ISS. Further, the immune response to specific target antigens can be induced by administration of an antigenic molecule in association with lipid particles containing such non-sequence specific oligodeoxynucleotides.

## II. ARGUMENT

### REJECTION UNDER 35 U.S.C. §103 OVER KRIEG ('646) OR KRIEG ('199), TAKEN WITH ANY OF WHEELER *ET AL.* ('501), MACLACHLAN ('741) OR SEMPLE ('278) SHOULD BE WITHDRAWN

#### A. The Examiner Has Not Established a *Prima Facie* Case of Obviousness

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claimed limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the Examiner has failed to establish at least two of these criteria, and thus a *prima facie* case of obviousness has not been set forth in the instant case.

### 1. A Motivation or Suggestion to Combine is Lacking

The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. To support the conclusion that the claimed invention is directed to obvious subject matter, the references must expressly or impliedly suggest the claimed invention, or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention to be obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Neither basis for combining the cited references has been properly established in the present case.

#### a. No Motivation Can be Drawn from the References Themselves

With respect to the first basis for combining, there is no motivation or suggestion in the references themselves to combine their teachings as proposed. The Krieg references very generally describe a wide variety of potential delivery options for their immunostimulatory nucleic acids, including a non-specific suggestion of "nucleic acids associated with: . . . a lipid (e.g. a cationic lipid, virosome or liposome)." ['646 Patent, Col. 12, ll. 30-33]. As the Examiner

admits, however, neither of the Krieg patents include any teaching, suggestion or motivation to fully encapsulate their immunostimulatory nucleic acids within a lipid particle as presently claimed. [Office Action mailed 10/7/04, p. 11]. Indeed, lipid-based delivery is proposed only in passing, embedded among a number of other possibilities, none of which are exemplified.

Clearly, neither Krieg reference would motivate the skilled artisan to select any particular lipid delivery vehicle from the genus of "nucleic acids associated with a lipid," any more than one of the myriad other vehicles disclosed therein, including sterols ('199 patent, col. 14), target cell specific binding agents ('199 patent, col. 15), coupling or crosslinking agents such as protein A, carbodiimide, and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) ('199 patent, col. 22) or virosomes ('199 patent, col. 22). Instead, the preferred embodiments actually disclosed in the examples utilize phosphorothioate-modified oligodeoxynucleotides in simple intraveneous solutions, which is clearly set forth as the preferred embodiment. Accordingly, neither of the Krieg patents even impliedly suggest the claimed invention, let alone expressly do so. *See In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1990) (finding no motivation to combine where the prior art reference disclosed a vast number of possibilities and gave as a preferred embodiment different compositions).

Conversely, there is also no mention or suggestion in the cited lipid patents that they could or should be employed for the delivery of immune stimulatory nucleic acids. To the contrary, the references relied on by the Examiner are more generally directed to the disparate therapeutic field of gene and antisense therapy, where the clear stated objective is to reduce if not substantially eliminate any immune response. There is certainly no motivation to be drawn from any of these disclosures to support their combination with the immunostimulatory nucleic acids

of Krieg. To the contrary, the divergent therapeutic objectives of these sequence-specific therapeutic applications actually undercut any such motivation to combine.

Specifically, the Wheeler and MacLachlan references are both directed to gene therapy (*i.e.*, sequence-specific) applications, which explicitly teach to reduce immunogencity and consequent elimination by the host immune system. [*See, e.g.*, MacLachlan at p. 18, lines 11-22; Wheeler at p. 35]. As the Examiner has previously admitted, the stated objective of Semple in reducing the immune clearance of their disclosed antisense therapeutics also conflicts with the immune stimulatory objective of the present case:

> **On the contrary, the parent application, when read as a whole,** clearly envisions **the advantages in utilization of** encapsulated cationic amphiphile/**antisense** complexes **mainly by their lesser clearance response.** The intended application of an encapsulated cationic lipid/antisense DNA . . . neither supports in any way a broader genus of any encapsulated cationic lipid/nucleic acid polymer complexes for use as an immunostimulatory composition, let alone other specific claimed limitations which recites CpG motifs and secretion of a cytokine ...

[Office Action mailed 3/27/03, U.S. Appln. S/N 09/649,527, p. 3 (emphasis in original)]. The Examiner has taken a similar position in the instant application, (Office Action mailed 12/22/03, p. 5). This same disparity in the basic biological objectives of immune stimulation versus gene and antisense therapy also undercuts any alleged motivation to combine the cited lipid encapsulation references with the immune stimulatory nucleic acids taught by Krieg.

Accordingly, Applicants respectfully submit that the requisite motivation or suggestion to combine the immune stimulatory nucleic acids of Krieg with the gene therapy lipid vehicles of Wheeler, MacLachlan and/or Semple cannot be properly drawn from their disparate disclosures, and thus a *prima facie* case of obviousness cannot be established on this basis.

**b. The "Totality" of the Prior Art is Also Not Supportive of the Examiner's Obviousness Rejection**

With respect to the second basis, the Examiner also failed to present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention obvious in light of the teachings of the references. The Examiner's general assertions that "the art of making lipid particle comprising a cationic lipid as a carrier in encapsulating a bioactive agent such as DNA is well known in the prior art," (Office Action mailed 5/6/05, p. 3), are an inadequate and inappropriate basis for rejecting the presently claimed invention, as well as being inaccurate. *See In re Dembizak*, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.") Reliance on a high skill level in the art as a justification for a proposed combination is equally improper. *See In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998) (PTO erred in finding suggestion or motivation to combine prior art references based solely on the high level of skill in the art). Moreover, and contrary to the Examiner's assertion, Applicants are not ignoring the "totality"of the prior art in arguing against the Examiner's rejection. Rather, Applicants maintain that the totality of the prior art is not supportive of the Examiner's obviousness rejection of the presently-claimed invention, including prior art that the Examiner thus far refuses to consider.

Implicit in the Examiner's position is the erroneous assumption that all lipid-based delivery vehicles will work the same for every therapeutic molecule and for any desired indication, an assumption clearly disproven by the data provided by Applicants in the specification and again by way of declaration. As the Examiner can appreciate, there are myriad types of liposomal delivery vehicles, having a wide variety of components, and capable of delivering a range of therapeutic molecules to different locations and cells in the body.

Necessarily, changing the lipid vehicle changes the pharmacodynamics and pharmacokinetics of the associated therapeutic molecule, and by altering the lipid composition the therapeutic agent can be targeted to particular cell types and can further be released extracellularly or intracellularly, depending on the properties and site of action of the particular therapeutic.

Accordingly, Applicants respectfully submit that the Examiner's stated reliance on the "totality of the art" and broad characterizations of the liposome field is overly simplistic and ignores important differences in the structure and composition of the presently-claimed compositions that lead to significantly improved results. The issue presented for decision herein is not whether lipid vehicles were known for DNA delivery in general, but rather whether Applicants' selection of the particular lipid vehicle claimed herein and the resulting discovery of the synergistic enhancement of immunostimulatory activity of fully encapsulated ISS ODN are nonobvious and unexpected in view of the totality of the art. Applicants maintain that they are. The Examiner's rejection overlooks the complexity of lipids as a class of delivery vehicles and erroneously assumes that one size liposome fits all therapeutic agents, including agents having a completely uncharacterized mechanism of action.

At best, the simple statement in Krieg that their CpG oligonucleotides could be associated with "a sterol," "a lipid" or "a target cell specific binding reagent," Krieg, column 12, lines 31-35, is merely an invitation to the skilled artisan to engage in hit-or-miss experimentation on an almost limitless number of possible delivery options, with little or no guidance or direction, and without any understanding of the underlying mechanism or site of action of the particular therapeutic agent at issue. This suggests a classic obvious-to-try situation, where "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either

no indication of which parameters were critical or no direction as to which of many possible choices is likely to be explored." *See In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Thus, to the extent that the Examiner is asserting based on Krieg it would have been obvious to try delivering immunostimulatory oligonucleotides in lipid delivery vehicles such as the particular lipid vehicles described and claimed by Applicants, this argument is improper and also does not support the Examiner's obviousness rejection based on the cited references.

**c. Conventional Wisdom as of the Priority Date was to Employ Cationic Lipid / DNA Complexes for Immunostimulatory Purposes**

If anything, the totality of the prior art suggests an entirely different solution than that pursued by Applicants. In this regard, the Examiner is directed again to the teachings by Dow *et al.*, who published contemporaneous academic articles in addition to the patent disclosures previously submitted by Applicants. Dow *et al.*, *J. Immunol.* 163:1552-61 (1999) (included as document C2 in the accompanying Supplemental IDS). These references provide a clear teaching to the skilled artisan that immune stimulatory oligonucleotides complexed with cationic lipids provided potent immune activation. The Dow group's complexation approach is further consistent with the previous teachings by Zelphati and others, who taught that lipid complexes were sufficient to protect against serum nucleases. Zelphati and Szoka, *J. Lip. Res.* 7:31-49 (1997) (included as document C6 in the accompanying Supplemental IDS). Indeed, Zelphati *et al.*. further suggested to the skilled artisan in 1997 that "in contrast to all other types of liposomes, cationic liposomes do not require any encapsulation step that limits the application of these carriers." *Id.*

Applicants respectfully submit that these clear teachings with respect to lipid-based delivery of immune stimulatory DNA coupled with the absence of any other more relevant disclosures plainly demonstrate that the conventional wisdom in the liposome field as of the priority date of the instant case was systemic delivery of immunostimulatory oligonucleotides using cationic lipid complexes. In this regard, the Examiner is reminded that a person of ordinary skill in the art is "one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate . . . ." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 USPQ 293 (Fed. Cir. 1985).

As the Federal Circuit recently noted, a critical step in analyzing the patentability of claims under §103 is casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *In re Kotzab* , 208 F.3d 1352, 54 UPSQ2d 1308 (Fed. Cir. 2000). Close adherence to this methodology is particularly important in cases where the very ease with which the invention can be understood may prompt one to fall victim to hindsight wherein only that which the invention taught is used against is teacher. *Id.* Applicants' invention as presently claimed went against the conventional wisdom of lipid-nucleic acid complexation, a fact which is strongly indicative of nonobviousness.

**2. There Was No Reasonable Expectation of Success with Respect to the Effectiveness of the Lipid / Nucleic Acid Composition as Presently Claimed**

As noted above, in rejecting the presently-claimed invention the Examiner selectively relies on Applicants' own art describing encapsulation of therapeutic genes and antisense molecules in lipid formulations, which all have in common the objective of delivering these

sequence-specific nucleic acids to the nucleus of a target cell.[1] Certainly, the requisite site of action for these types of therapeutic molecules was known and thus researchers were better able to develop lipid formulations to get them to their destination. Nevertheless, although there was general consensus at the time regarding the desired target site there was still active investigation and debate regarding the mechanism by which lipid vehicles released oligonucleotides into cells, and there were a number of obstacles still to overcome. *See, e.g.* Zelphati, *supra* ("Cationic liposomes are a useful in vitro but as yet unproven in vivo delivery mechanism."); Hope *et al.*, *Mol. Membrane Biol.* 15:1-14 (1998) ("The ill-defined nature and unpredictable behavior of the resulting [cationic lipid/DNA] particles are major hurdles to overcome in generating non-viral, genetic pharmaceuticals.") (included as document C4 in the accompanying Supplemental IDS). These contemporaneous statements from skilled artisans in the field of liposomal delivery vehicles are directly contrary to the Examiner's position that such compositions are "routine and conventional" in the art. Indeed, even where the site and mechanism of action of the therapeutic DNA was known, there was still significant debate among scientists as to the most efficacious way to deliver these therapeutics and considerable variability in such formulations.

In marked contrast to the antisense and therapeutic genes contemplated in the Examiner's selected art references, the underlying mechanism of action and requisite delivery profile for ISS such as CpG oligonucleotides was by no means certain at the priority date of the instant case. In fact, the search for the elusive ISS receptor was still ongoing at the time and there was evidence of both cell-surface and intracellular signaling. Hemmi *et al.* at p. 743. In formulating the pending rejection the Examiner is also erroneously assuming that the delivery of ISS should necessarily follow the same path as the delivery of sequence-specific nucleic acids, an

[1] In this regard, Applicants have reconsidered and concur with the Examiner's position that Wheeler *et al.* discloses

assumption we now know to be incorrect. More to the point, however, as of the priority date of the instant case no one knew the site of action of the ISS and thus the skilled artisan was left to speculate on the most appropriate formulation, lipid or otherwise.

Given the uncertainties and challenges with respect to *in vivo* lipid delivery noted by skilled artisans in the contemporaneous art references above, and the complete absence of knowledge of the mechanism and/or site of action of immune stimulatory oligonucleotides as of the priority date of the instant case, Applicants respectfully submit that there is an inadequate factual basis to support a reasonable expectation of success with the presently-claimed compositions. Quite simply, without trying it, one would not know whether it works. If anything, the successes claimed by researchers such as Dow *et al.* with cationic lipid/DNA complexes pointed to complexation, rather than encapsulation, as the better approach.

**B. Applicants' Evidence of Superior and Unexpected Results Rebuts Any *Prima Facie* Case of Obviousness**

Assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants have nevertheless rebutted any such case with their evidence of unexpectedly superior results. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed invention shares with the prior art, can rebut *prima facie* obviousness). Thus far, the Examiner has largely ignored Applicants' data and arguments in this regard. The Federal Circuit has emphatically and repeatedly held that objective evidence of nonobviousness must always be taken into account and not just when the decision maker is in doubt: "objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered

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liposome encapsulation as opposed to complexation.

before a conclusion on obviousness is reached." (*Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). *See also Bausch & Lomb, Inc. v. Barnes Hindes, Inc.*, 230 USPQ 416 (Fed. Cir. 1986); *Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984)).

As noted previously above, the most recent and pertinent teachings in the art directed specifically to the present field of invention, that is, the combination of lipids and nucleic acids for immune stimulatory purposes, teach that complexation rather than encapsulation provides a synergistic benefit. *See* Dow *et al.*, *supra*. Dow *et al.* teach that nucleic acid:lipid complexes are significantly more immunostimulatory than DNA administered alone (*i.e.* naked DNA as exemplified by Krieg), and that DNA from any source when complexed with lipids at low doses can synergize to provide a strong immunostimulatory effect. *Id.* Indeed, in their corresponding patent disclosures Dow *et al.* assert that their lipid complexes provide synergistic benefits. *See, e.g.,* U.S. Patent No. 6,693,086, submitted previously. Despite these alleged successes, however, the compositions described and claimed by Applicants were still shown to be at least four- to ten-fold more active in stimulating immune responses compared to the nucleic acid:lipid complexes taught by Dow and others. *See* Declaration of Michael J. Hope submitted June 23, 2004. In addition, the lipid encapsulated nucleic acid particles were shown to be much more effective in rendering the test animals tumor-free than the nucleic acid:lipid complexes. *Id.* These profound differences in immunostimulatory activity and tumor efficacy are proof of the superior and truly synergistic immune stimulatory properties resulting from the claimed lipid encapsulation approach, which compels a finding of nonobviousness.

For the foregoing reasons, Applicants respectfully request withdrawal of the Examiner's rejection of Claims 1, 3, 5-8, 11, 14, and 16-19 under 35 U.S.C. §103 based on the combination proposed above.

**REJECTION UNDER 35 U.S.C. §103 OVER KRIEG ('646) OR KRIEG ('199), TAKEN WITH ANY OF WHEELER *ET AL.* ('501), MACLACHLAN ('741) OR SEMPLE ('278), AND FURTHER IN VIEW OF MEERS ('716) SHOULD BE WITHDRAWN**

The claims are non-obvious over Krieg ('646) or Krieg ('199), taken with any of Wheeler *et al.* ('501), MacLachlan ('741) or Semple ('278), for the same reasons set forth in the preceding paragraphs.

The Examiner further cites the Meers patent as prior art. Applicants maintain that the Meers patent is directed principally to peptide-lipid conjugates and their use in liposomes. It has very little relevance to the claimed invention since it does not describe with any specificity the making of a lipid-nucleic acid composition, let alone the lipid-encapsulated nucleic acid compositions as claimed. In addition, it does not cure the deficiencies of the other references as discussed above. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as well.

## CONCLUSION

In conclusion, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness. Moreover, even if a *prima facie* case of obviousness has been established, Applicants have submitted ample evidence of the unexpected superiority of the claimed invention in an inducing immune response, which rebuts any such *prima facie* case and compels a finding of nonobviousness.

As such, Applicants respectfully request that the rejections be withdrawn.

Respectfully submitted,

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